



Addiction

CPC Zurich 2021



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Outline

- *Substance use, disease burden, harm of different drugs*
- *Opioid Epidemic: Evidence vs. Practice in Addiction medicine (or politics)*
- *Dependence Syndrom: (Categorical) Definition and related challenges*
- *Factors leading to addiction*
- *Neurobiological changes associated with addictive behavior*
- *Translational aspects of addiction research*

Risk factor	Mean rank (95% UI)	% change (95% UI)
1 High blood pressure	1·1 (1-2)	27% (19 to 34)
2 Smoking (including SHS)	1·9 (1-2)	3% (-5 to 11)
3 Household air pollution	4·6 (3-7)	-37% (-44 to -29)
4 Low fruit	5·0 (4-8)	29% (25 to 34)
5 Alcohol use	5·1 (3-7)	32% (17 to 47)
6 High body-mass index	6·1 (4-8)	82% (71 to 95)
7 High fasting plasma glucose	6·6 (5-8)	58% (43 to 73)
8 Childhood underweight	8·5 (6-11)	-61% (-66 to -55)
9 Ambient PM pollution	8·7 (7-11)	-7% (-13 to -1)
10 Physical inactivity	10·0 (8-12)	0% (0 to 0)
11 High sodium	11·2 (8-15)	33% (27 to 39)
12 Low nuts and seeds	12·9 (11-17)	27% (18 to 32)
13 Iron deficiency	13·5 (11-17)	-7% (-11 to -4)
14 Suboptimal breastfeeding	13·8 (10-18)	-57% (-63 to -51)
15 High total cholesterol	15·2 (12-17)	3% (-13 to 19)
16 Low whole grains	15·3 (13-17)	39% (32 to 45)
17 Low vegetables	15·8 (12-19)	22% (16 to 28)
18 Low omega-3	18·7 (17-23)	30% (21 to 35)
19 Drug use	20·2 (18-23)	57% (42 to 72)
20 Occupational injury	20·4 (18-23)	12% (-22 to 58)
21 Occupational low back pain	21·2 (18-25)	22% (11 to 35)
22 High processed meat	22·1 (17-32)	22% (2 to 44)
23 Intimate partner violence	23·8 (20-28)	0% (0 to 0)
24 Low fibre	24·5 (19-32)	23% (13 to 33)
25 Lead	25·5 (23-29)	160% (143 to 176)
26 Sanitation		
29 Vitamin A deficiency		
31 Zinc deficiency		
34 Unimproved water		

— Ascending order in rank
 - - - Descending order in rank

Global Burden of Disease Study 2010

Most important risk factors

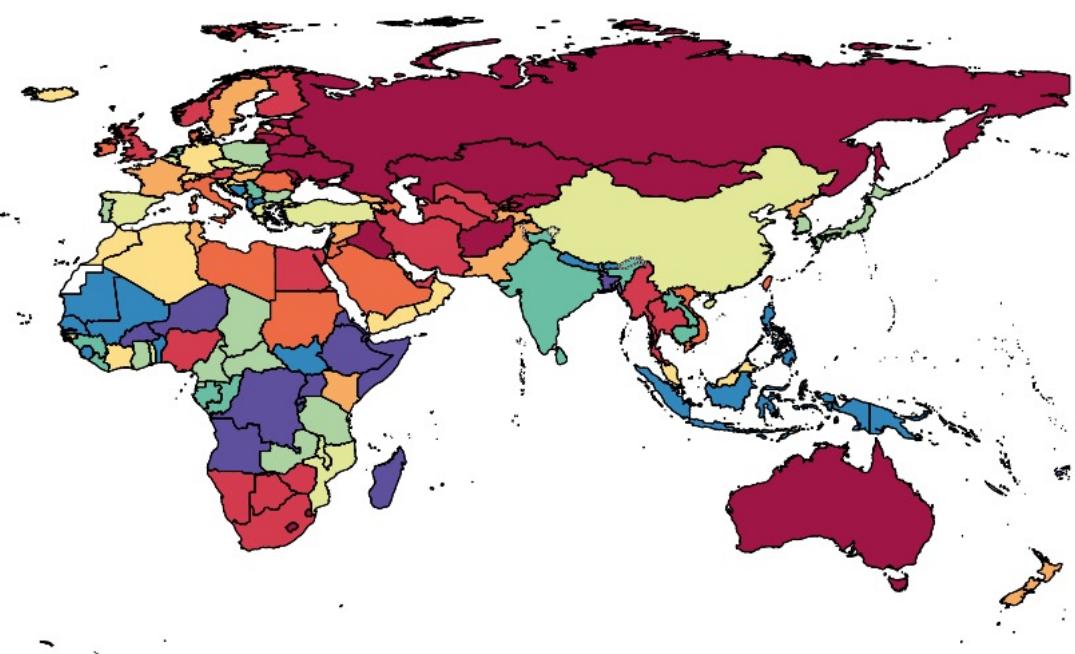
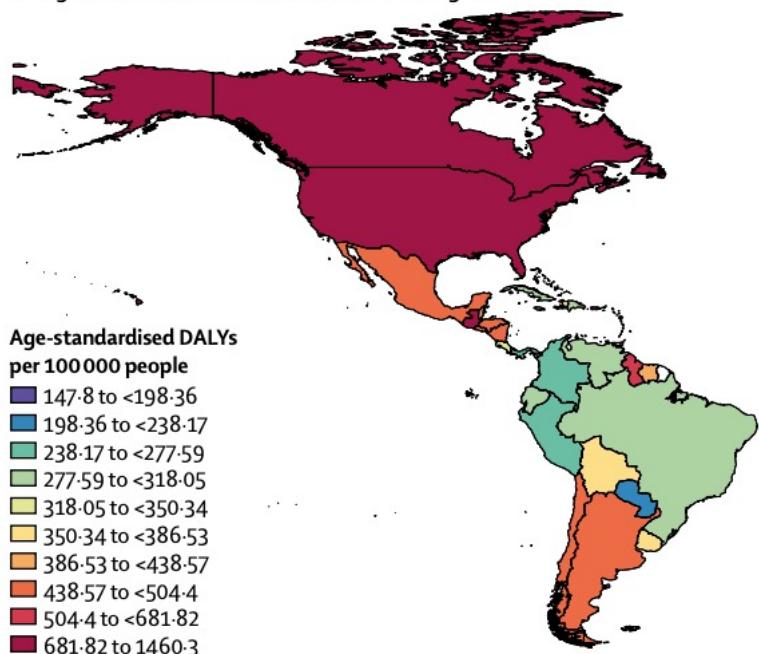
Lim et al., 2012
 The Lancet

„Alcohol and illicit drug use account for 5.4% of the world's annual disease burden, with tobacco responsible for 3.7%“ WHO ATLAS 2010

The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

GBD 2016 Alcohol and Drug Use Collaborators*

B Age-standardised DALYs attributable to drug use



Degenhardt et al., 2018
Lancet Psychiatry

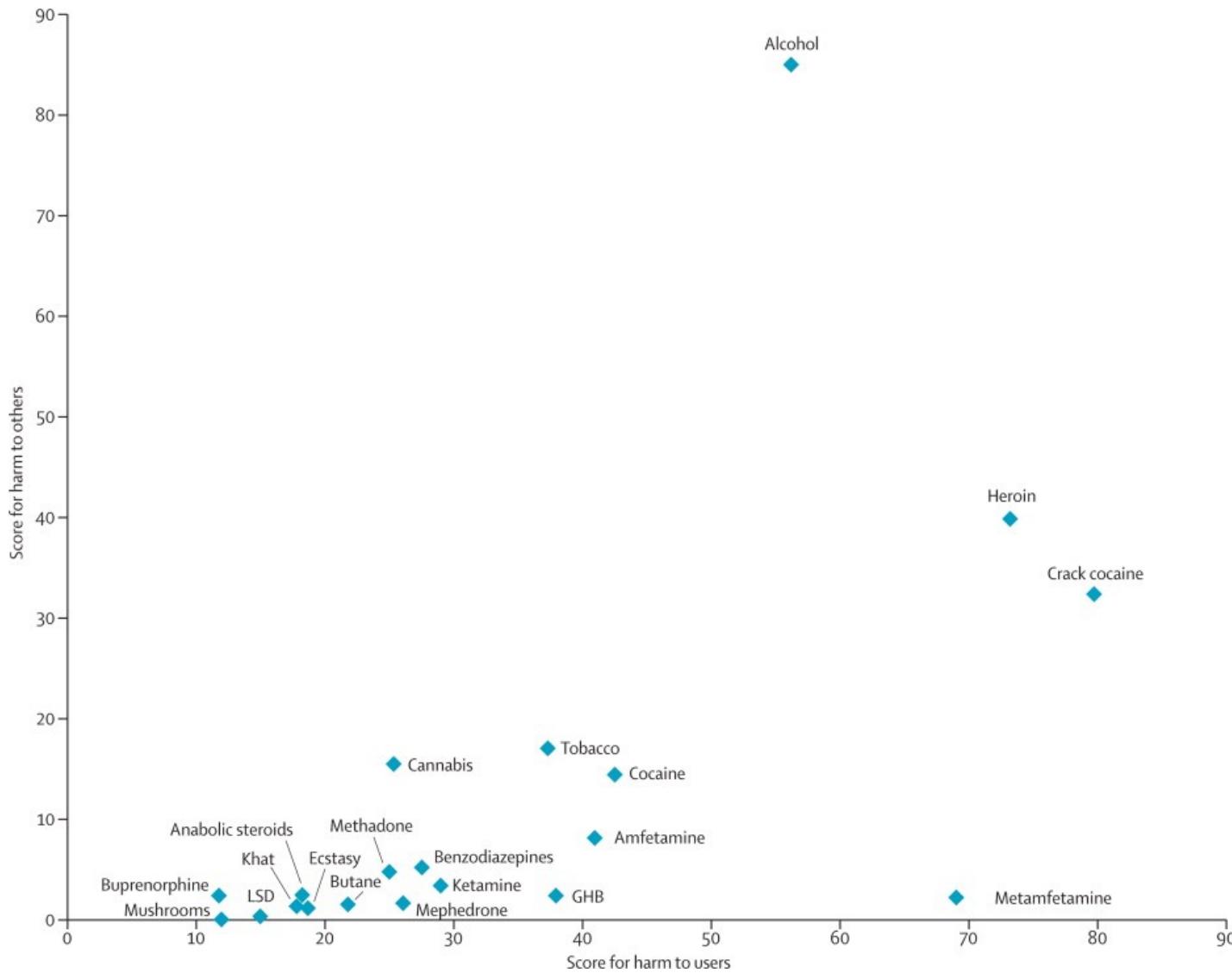
The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

GBD 2016 Alcohol and Drug Use Collaborators*

- ***Appr. 100 million people with alcohol dependence***
- ***Appr. 22 million people with cannabis dependence***
- ***Appr. 27 million people with opioid dependence***
- ***2016: appr. 100 million DALYs (disability adjusted life years; loss of years of full health through premature death or disability) due to alcohol and 31 million DALYs due to other drugs***

Degenhardt et al., 2018
Lancet Psychiatry

Harm related to different drugs

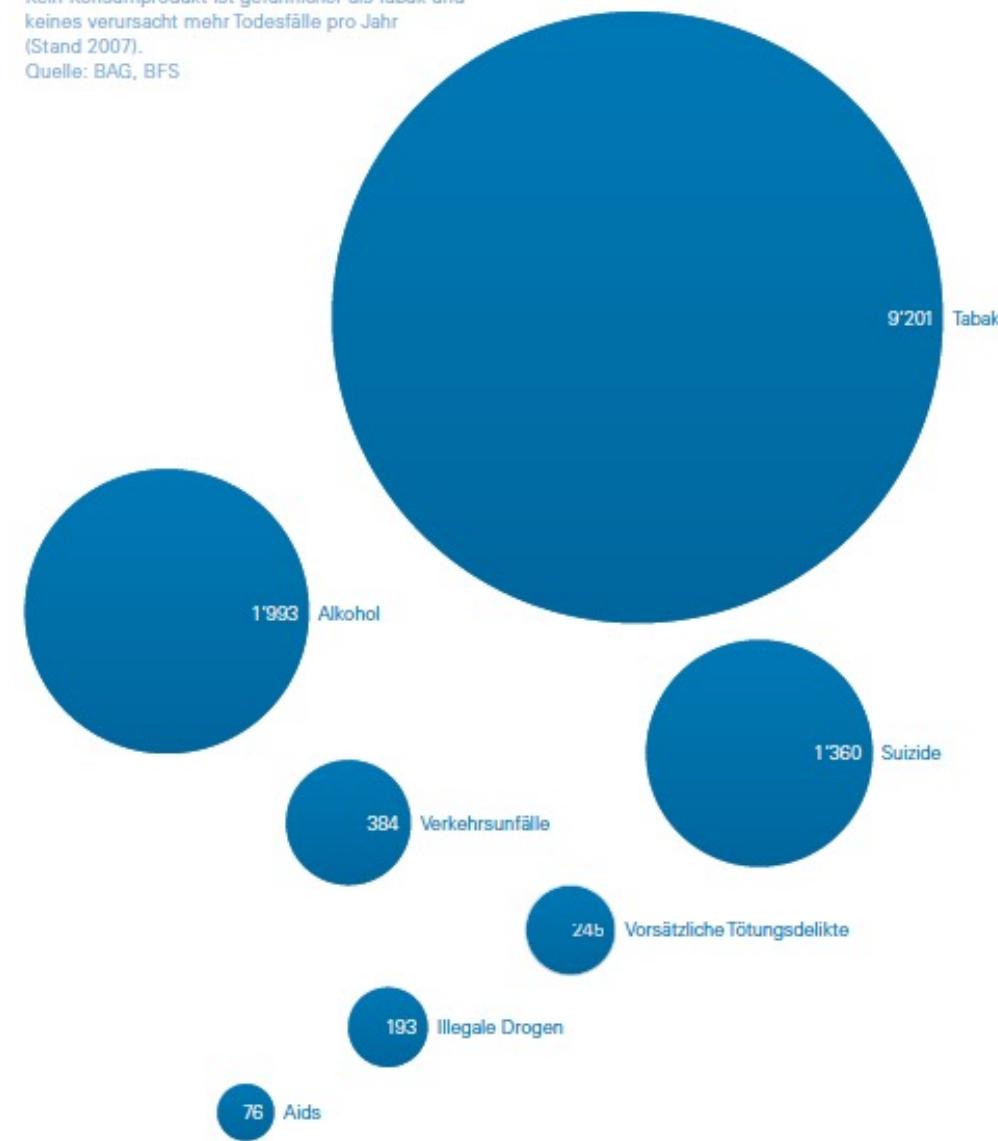


Nutt et al. The Lancet 2010; 376:1558-1565



Main causes for premature and preventable mortality in Switzerland

Todesursachen in der Schweiz
In der Schweiz stellt der Tabakkonsum die Hauptursache für vermeidbare frühzeitige Todesfälle dar. Kein Konsumprodukt ist gefährlicher als Tabak und keines verursacht mehr Todesfälle pro Jahr (Stand 2007).
Quelle: BAG, BFS



9/10 people (>15yrs) in Switzerland drink alcohol

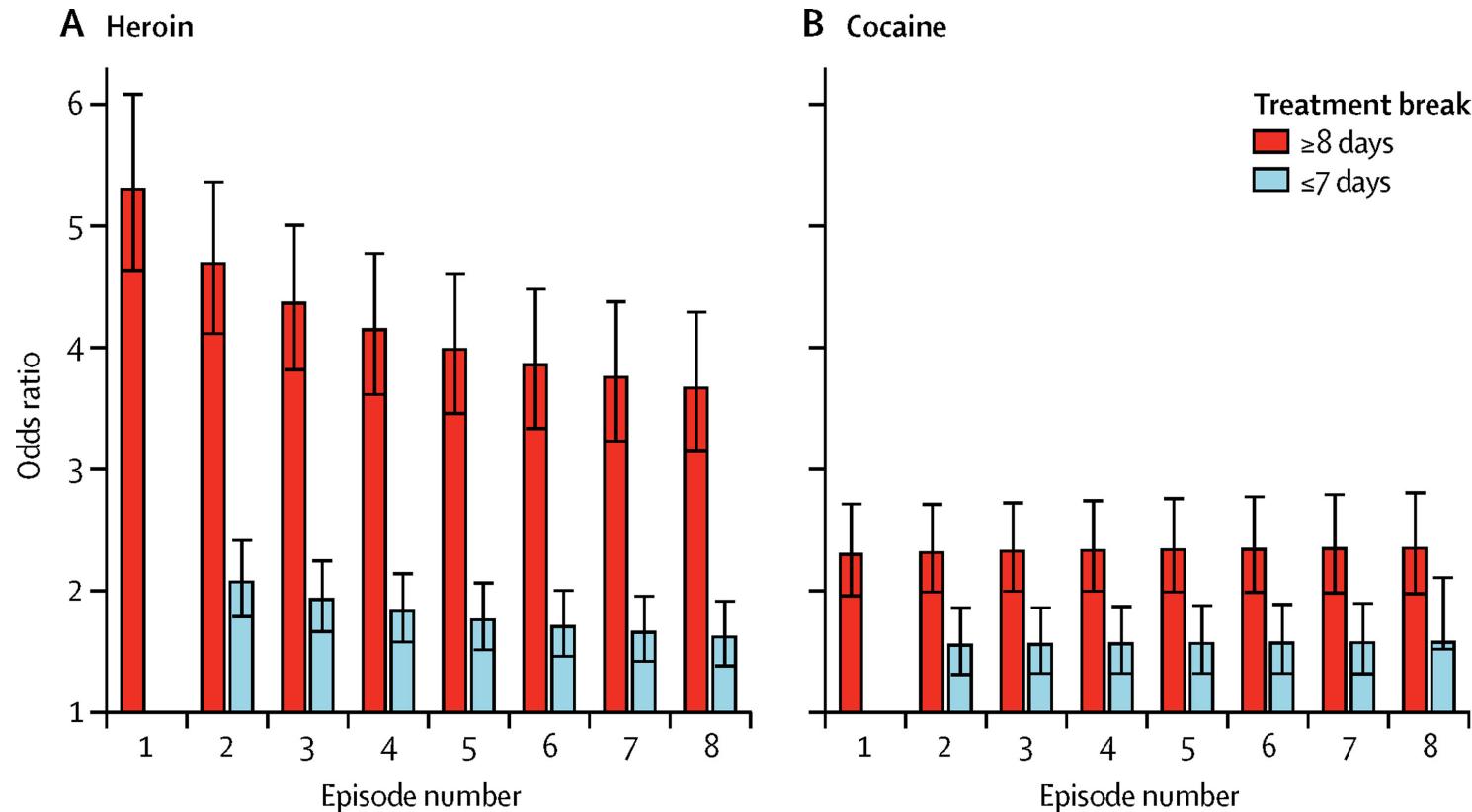
At least 8/10 people use alcohol at very low risk levels

Some alcohol users suffer from a state that is considered a mental disorder/disease, i.e. a clinically relevant condition characterised by psychological dysfunctions that are accompanied or result in individual harm and/or severe impairment of social participation (Heinz 2015, 2017)

Open drug scene in Zurich, 1980/90ies

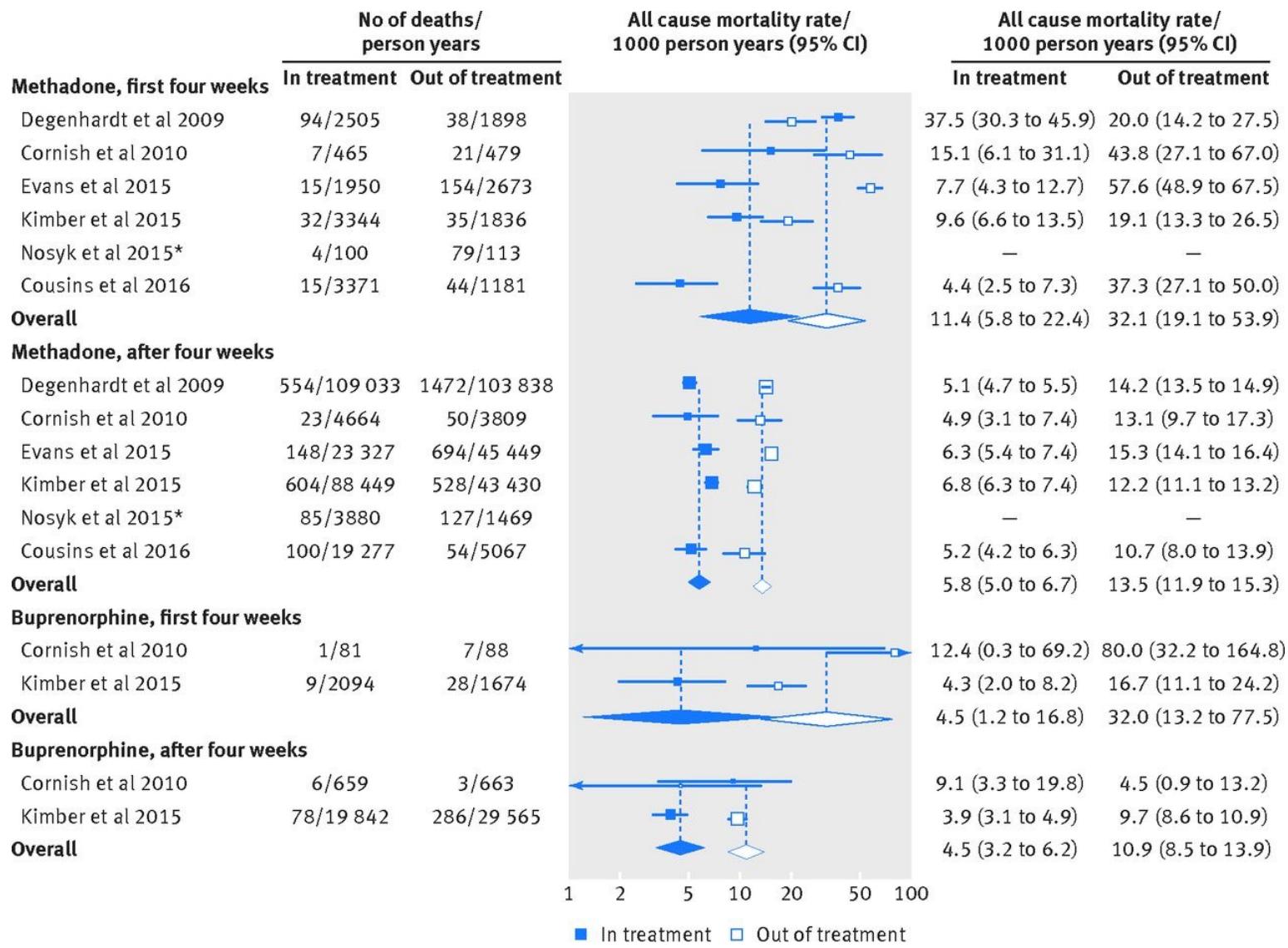


Heroin (and cocaine) use is substantially reduced in patients entering opioid agonist treatments



Mortality rates in and out of opioid substitution treatment with methadone or buprenorphine

Psychiatrische
Universitätsklinik Zürich



thebmj

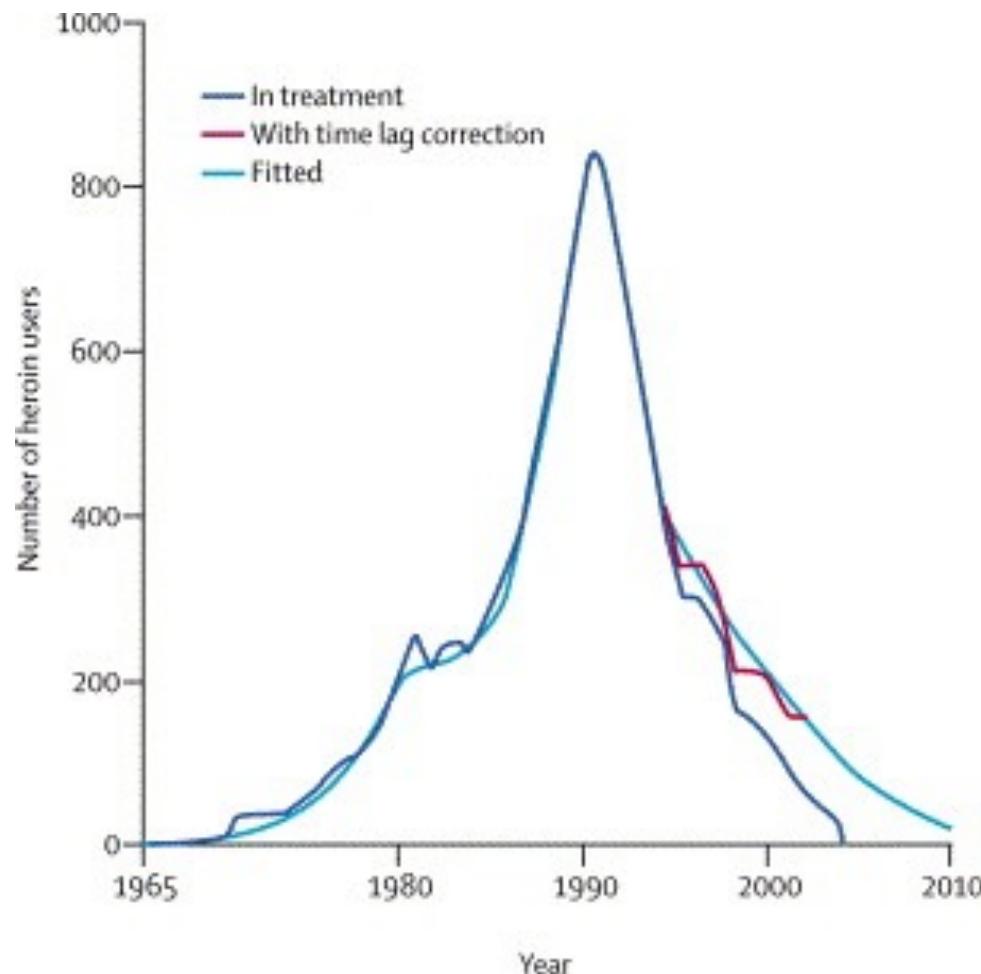
ersität
Zürich

Opioid agonist treatment („substitution therapy“)

- Good evidence for the efficacy of opioid agonist treatment (Cochrane review Mattick et al., 2009)
 - Reduction of heroin use (and cocaine use)
 - Reduction of (Co-)morbidity (infectious diseases etc.)
 - Reduction of mortality
 - Improve quality of life
 - Increases treatment retention
 - cost-efficient

“For most patients, opioid agonist maintenance treatment will result in better outcomes than attempts at withdrawal [...] In particular, patients on opioid agonist maintenance treatment are more likely than those not undergoing such treatment to stay alive, not use heroin, and be in contact with the treatment system” (WHO, 2009)

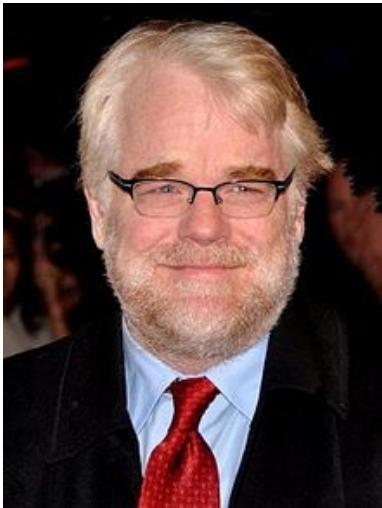
Incidence of heroin use in Zurich, Switzerland: a treatment case register analysis



Nordt and Stohler, Lancet, 2006

Zurich, Platzspitz today





„Inside a Killer Drug Epidemic: A Look at America’s Opioid Crisis
The opioid epidemic killed more than 33,000 people in 2015.“

New York Times, Jan, 2017

«Opioids were involved in 49,860 overdose deaths in 2019 (70.6% of all drug overdose deaths).» Center for Disease Control (CDC), 2020

Policy and Practice

The treatment gap in mental health care

Robert Kohn et al.

Table 2. Estimates of the median treatment gap (%) by WHO region

Mental disorder	WHO region					
	Africa	Americas	Eastern Mediterranean	Europe	South-East Asia	Western Pacific
Schizophrenia	NA ^a	56.8	NA	17.8	28.7	35.9
Major depression	67.0	56.9	70.2	45.4	NA	48.1
Dysthymia	NA	48.6	NA	43.9	NA	50.0
Bipolar disorder	NA	60.2	NA	39.9	NA	52.6
Panic disorder	NA	55.4	NA	47.2	NA	66.7
Generalized anxiety	NA	49.6	NA	62.3	NA	55.6
Obsessive compulsive	NA	82.0	NA	24.6	NA	62.7
Alcohol abuse/dependence	NA	72.6	NA	92.4	NA	71.6

^a Not available.

Kohn et al., 2004
 Bulletin of the WHO

Alcohol dependence: provisional description of a clinical syndrome

GRIFFITH EDWARDS, MILTON M GROSS

British Medical Journal, 1976, 1, 1058-1061

The American National Council on Alcoholism has recently analysed diagnostic criteria,² and a World Health Organisation group is preparing a report that seeks to define this syndrome and examine its importance.* Furthermore, we take the term syndrome to mean no more than the concurrence of phenomena. Not all the elements need always be present, nor always present with the same intensity. No assumptions need be made about the cause or the pathological process, though the obvious scientific challenge is to understand the underlying reasons for the clustering and covariance.

Essential elements of the syndrome

Essential elements might provisionally include: a narrowing in the repertoire of drinking behaviour; salience of drink-seeking behaviour; increased tolerance to alcohol; repeated withdrawal symptoms; repeated relief or avoidance of withdrawal symptoms by further drinking; subjective awareness of a compulsion to drink; reinstatement of the syndrome after abstinence. All these elements exist in degree, thus giving the syndrome a range of severity. They represent the dimensions along which the clinician can order the information given to him; one clinical element may reflect underlying psychobiological happenings of several types, and different clinical elements may be partial descriptions of the same underlying psychobiological process. In discussing the clinical presentations of each element we shall give particular attention to degrees of possible development and to patterning in presentation by personal and social factors.³



Implication for research and practice

The presumptive clinical identification of this syndrome has considerable significance for research; one important priority is the sharper delineation of the actual syndrome and of its natural histories and social settings—matters to which the everyday business of clinical observation, as well as more formal research, has much to contribute. Beyond this the research challenge is one of determining piece by piece the psychobiological basis. Better theoretical understanding should open possibilities of more effective treatment, in terms of attack on both biological and learning elements in the pathology.

More immediately an increased awareness of the diagnostic picture and of the need to see dependence in terms of degrees rather than absolutes may have some message for clinical practice. Again using an analogy, alcohol dependence may sometimes have been as loosely diagnosed as schizophrenia, with equally unfortunate consequences. Doctors should be aware that not every patient who drinks too much (for whatever reason) is necessarily dependent on alcohol, and different patients need different help and treatment. There has been some controversy about whether some alcoholics “can return to normal drinking”¹⁸ and whether abstinence should still be offered as the only treatment goal; the question may be sharper if applied not just to heterogeneous patient populations but separately to patients with different degrees of dependence. Some preliminary work does indeed suggest that the patients who are less dependent are those more likely to return to controlled drinking.¹⁹ The

Dependence syndrome (ICD-10)

- A strong desire or sense of compulsion to take the substance
- Impaired capacity to control substance-taking behaviour
- A physiological withdrawal state when substance use is reduced or ceased
- Evidence of tolerance to the effects of the substance (need for significantly increased amounts of the substance)
- Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use
- Persistent substance use despite harmful consequences

Three or more of the these manifestations should have occurred together for at least 1 month or, if persisting for periods of less than 1 month, should have occurred together repeatedly within a 12-month period

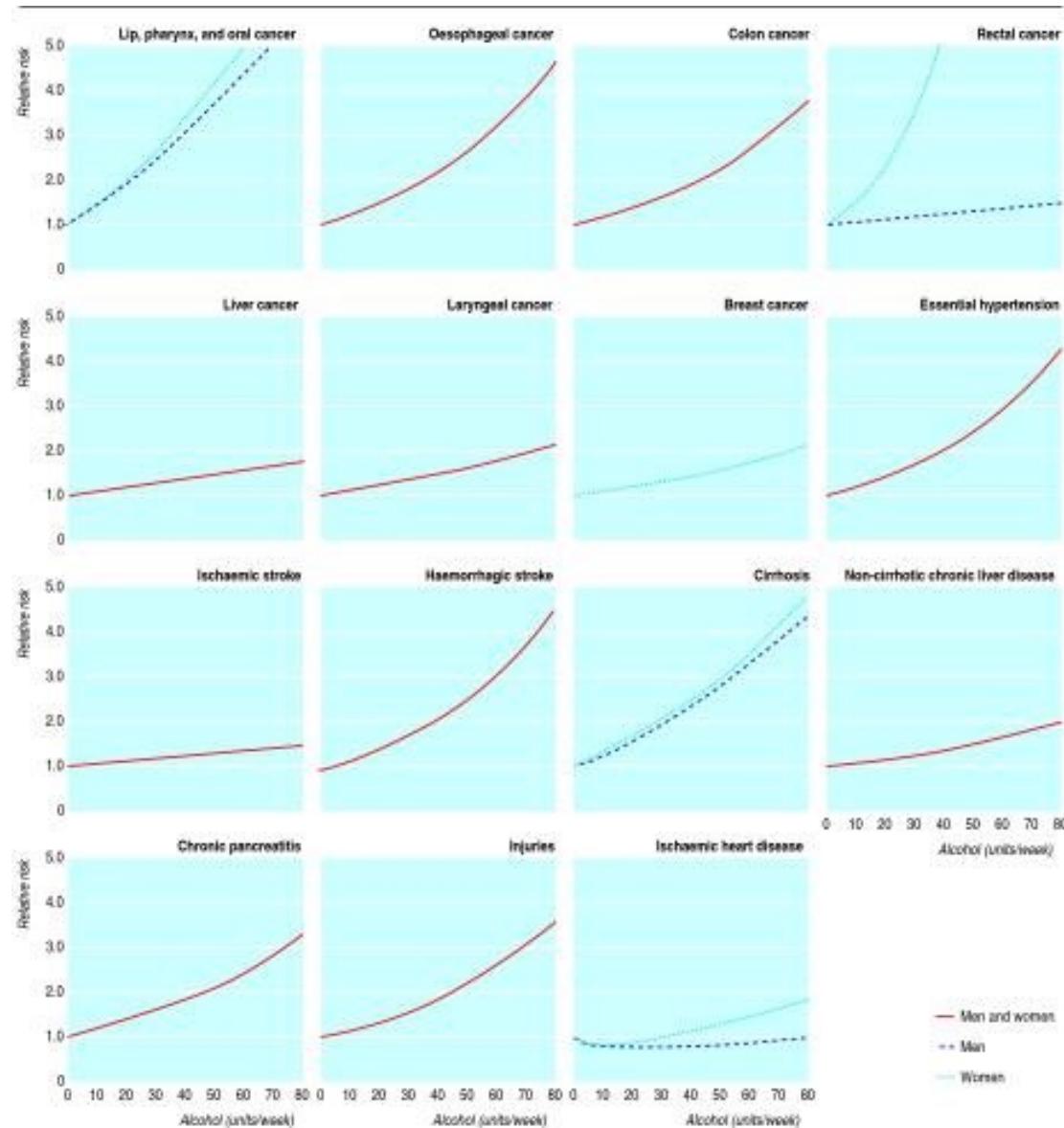
High reliability and psychometric validity of the dependence syndrom (Hasin, 2006)

Potential problems of categorical/binary classification systems (ICD/DSM):

- *heterogeneity within category is high (DSM-5 11 items, i.e. > 2000 potential combinations for fulfilling criteria of SUD)*
- *Probably easier for stigma to develop?*
- *Framework of binary thinking has impact not only on diagnosis but also on therapy and outcome measures*

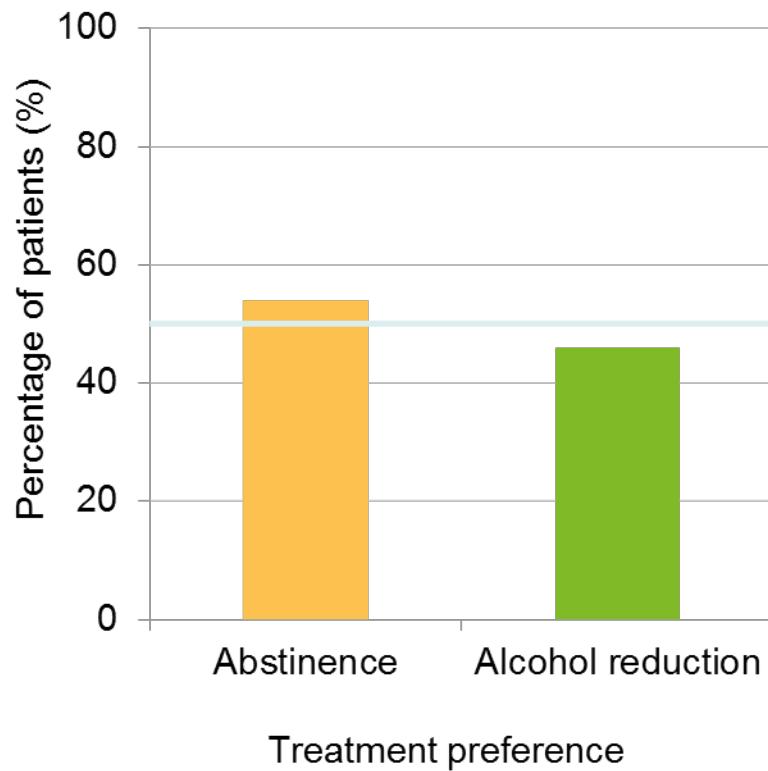


Relative Risk of somatic disease related to alcohol use

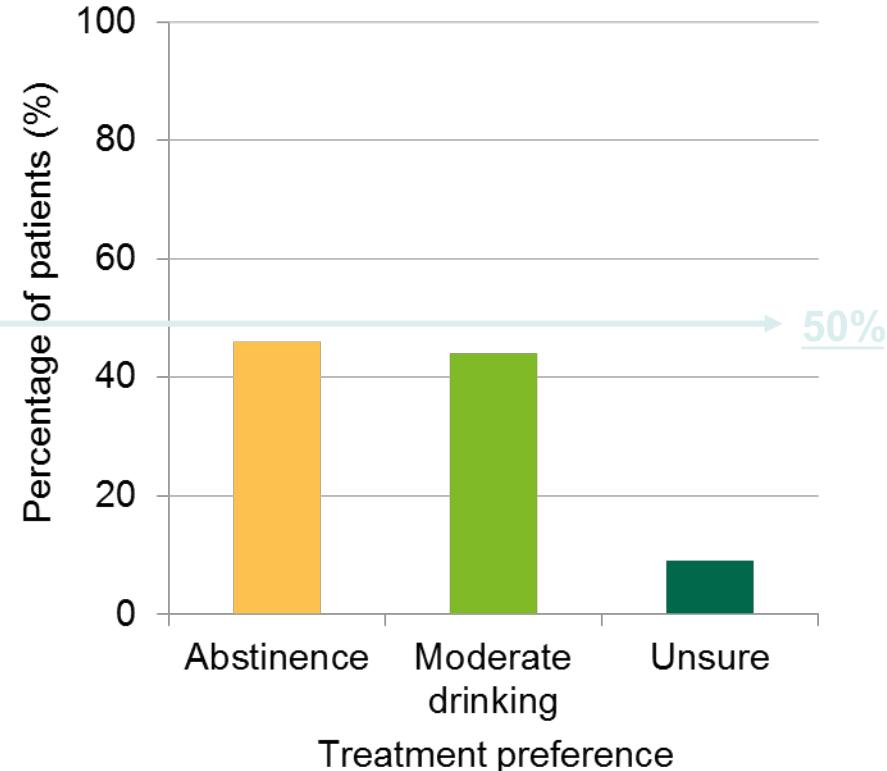


Therapeutic Outcomes – the patients' perspective

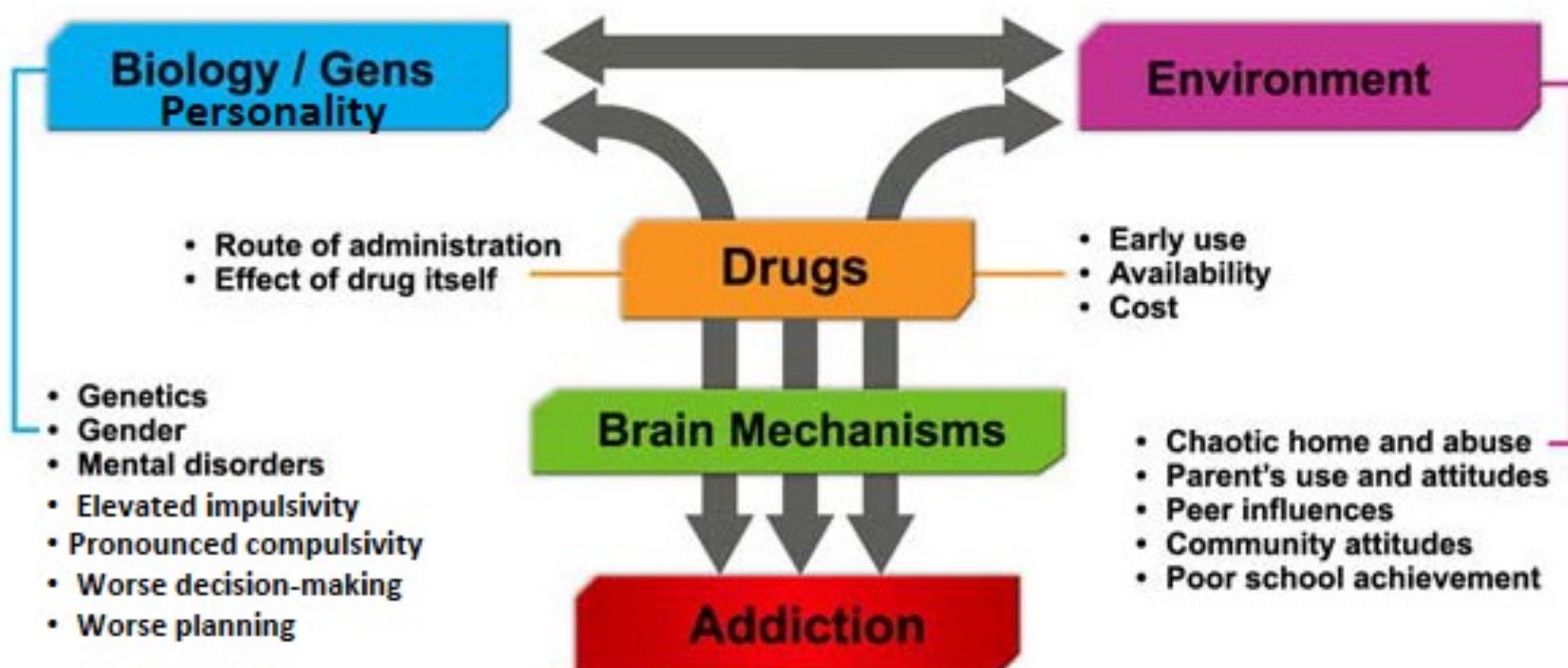
UK survey of patients with alcohol problems (n=742)



Canadian study of patients with chronic alcoholism (n=106)



Factors Leading to Addiction

NIDA, www.drugabuse.gov

From: Genetic and Environmental Influences on Alcohol, Caffeine, Cannabis, and Nicotine Use From Early Adolescence to Middle Adulthood

Arch Gen Psychiatry. 2008;65(6):674-682. doi:10.1001/archpsyc.65.6.674

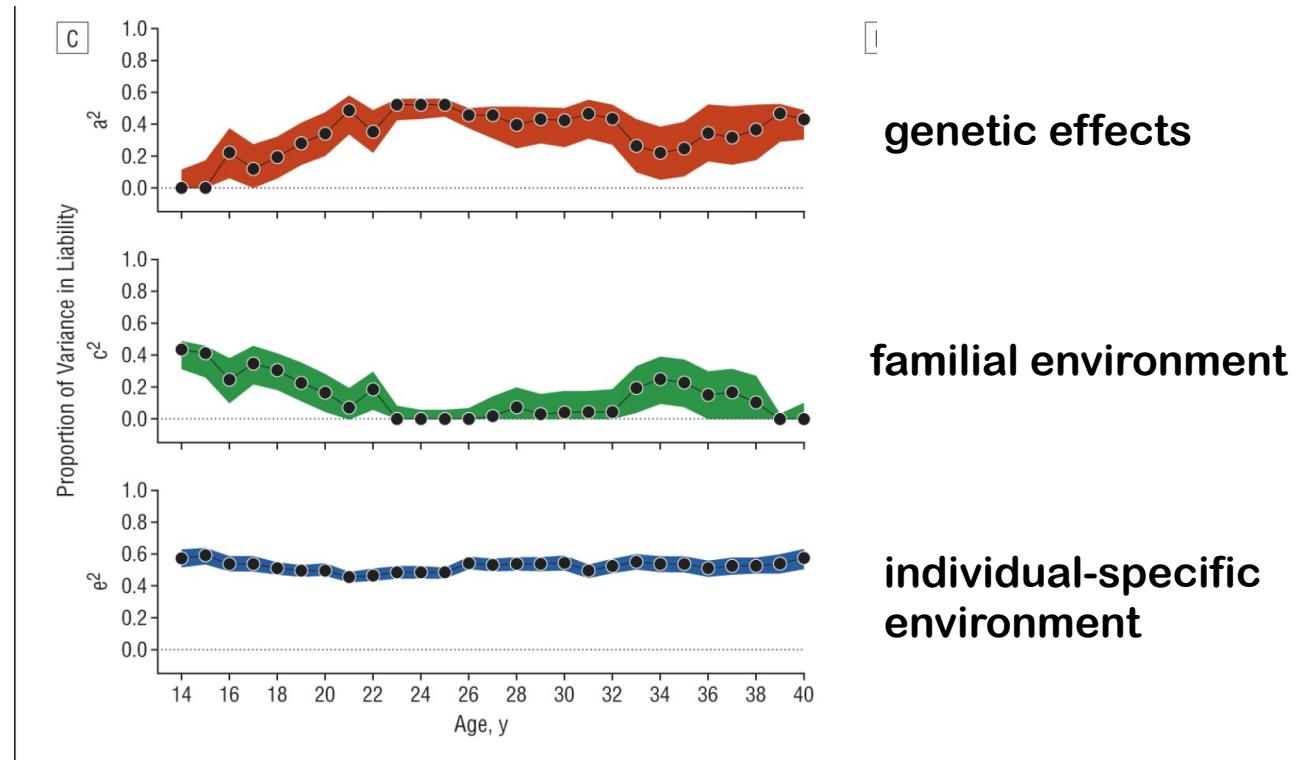
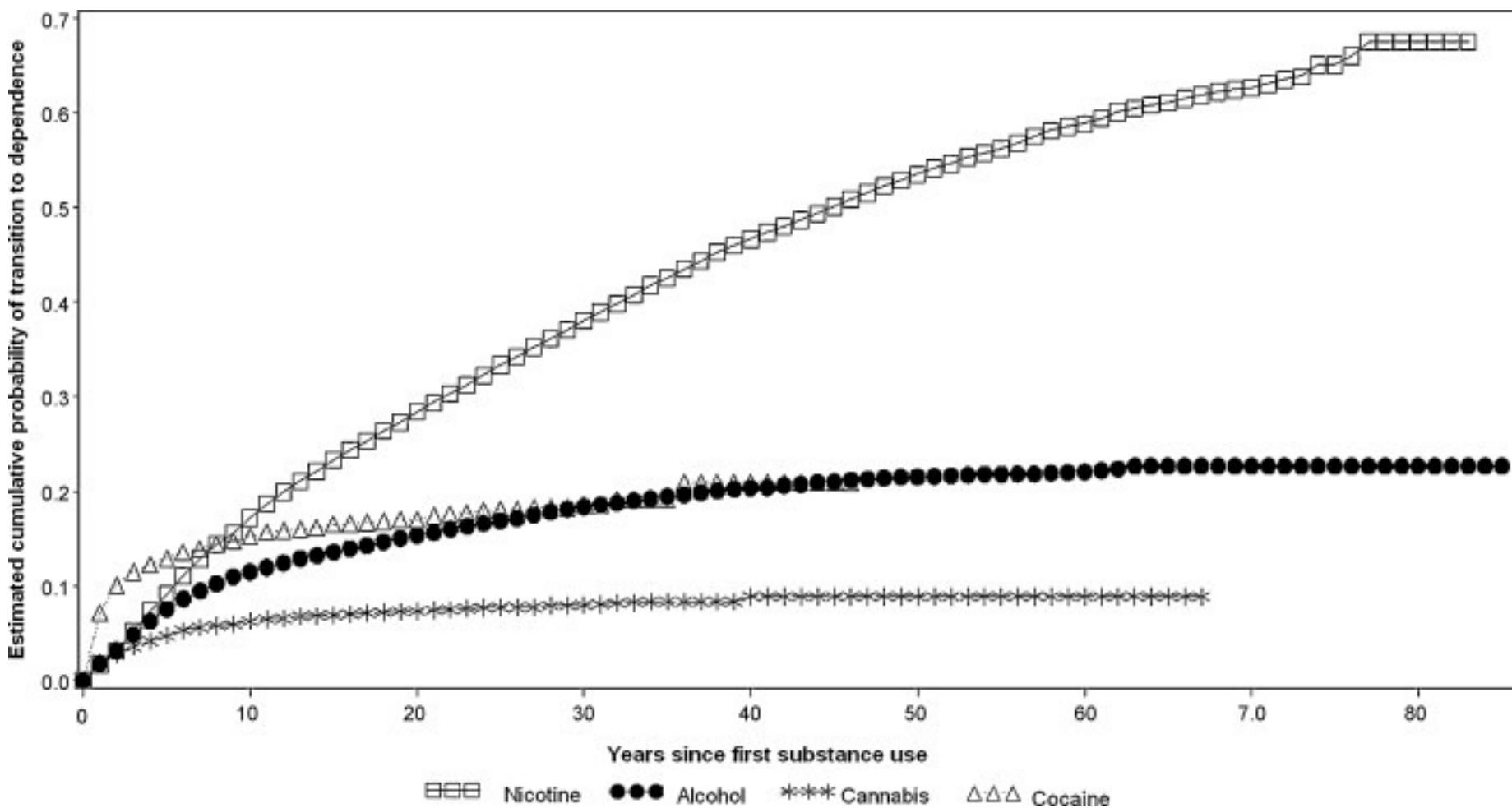


Figure Legend:

Parameter estimates \pm 1 SE for the contributions to variation in liability to psychoactive drug use of additive genetic effects (a^2), familial environmental factors (c^2), and the individual-specific environment (e^2) by year for the average daily number of caffeine-containing drinks for ages 9 to 35 years (A), the average daily number of cigarettes for ages 13 to 35 years (B), the average number of alcoholic drinks consumed per month for ages 14 to 40 years (C), and the average number of units of cannabis consumed per month for ages 14 to 35 years (D). The actual parameter estimates are depicted by the black lines, and the colored regions represent the possible range of estimates \pm 1 SE.

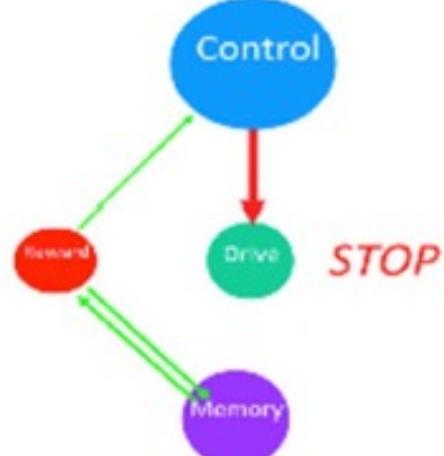
Proportion of users becoming dependent



Lopez-Quintero et al., Drug and Alcohol Dependence, 2011

Neuroadaptive changes in addiction

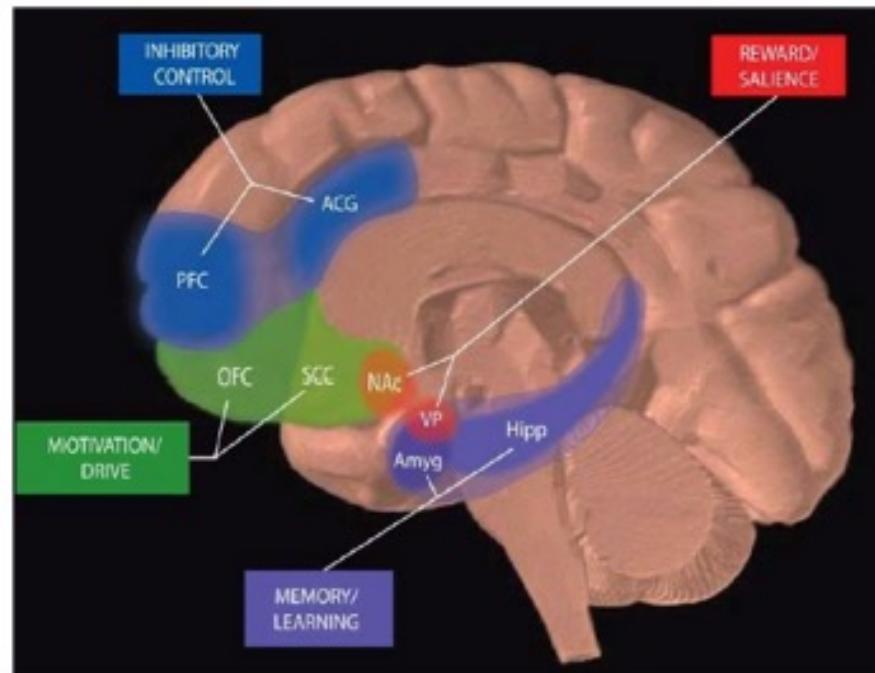
Nonaddicted Brain



Addicted Brain

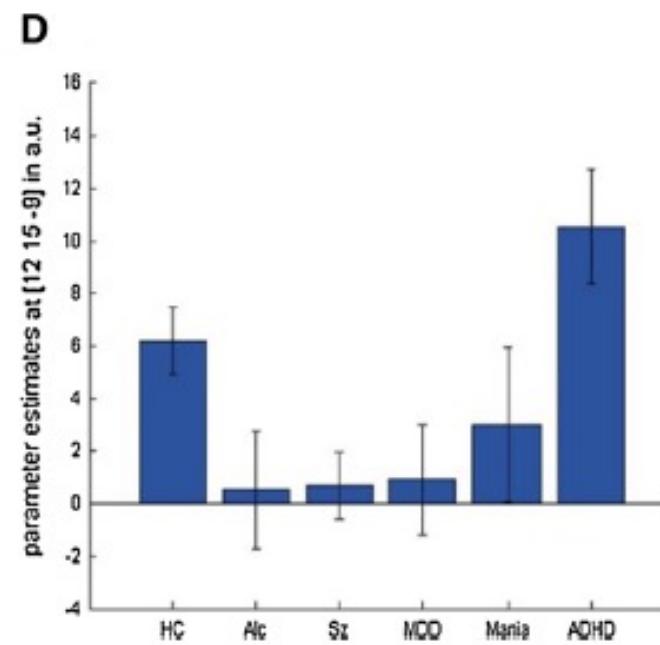
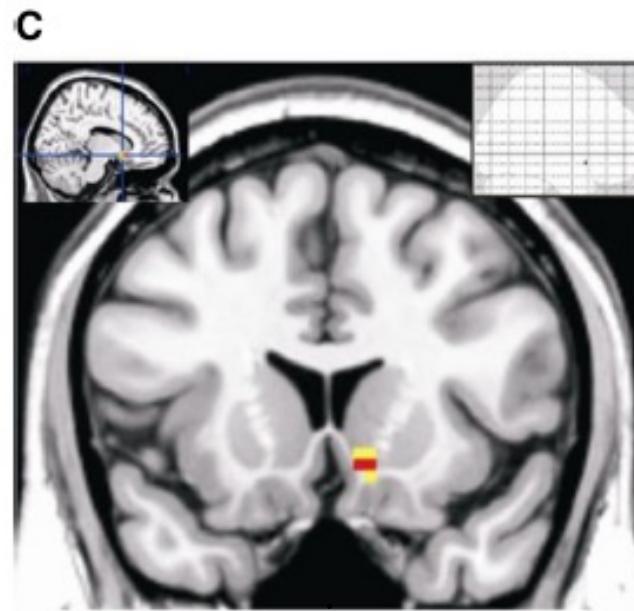
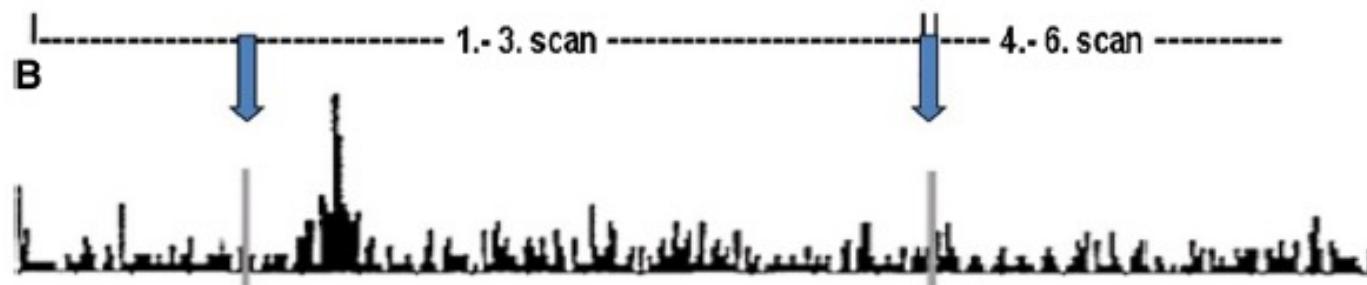
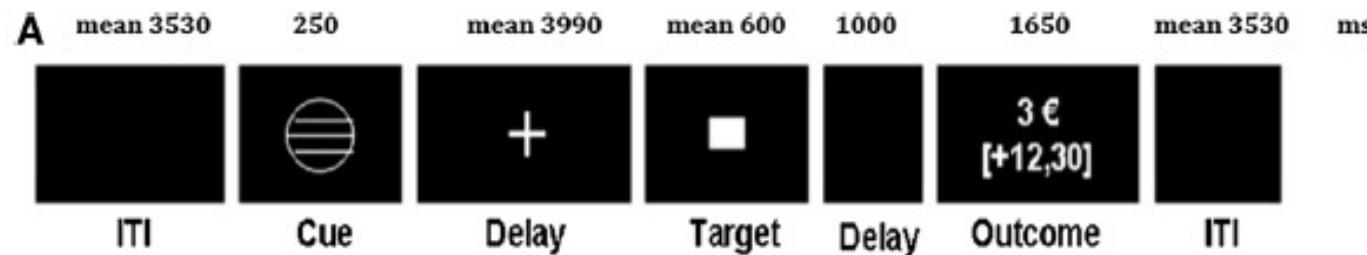


Volkow et al. 2011, Neuron



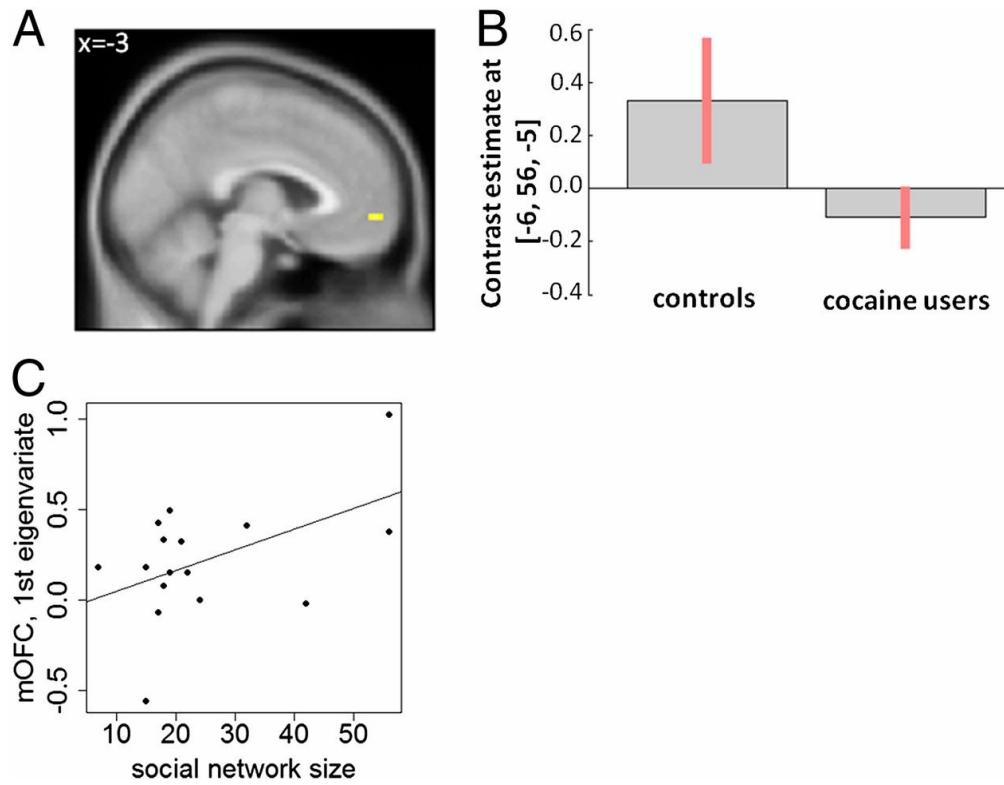
NIDA, www.nida.nih.gov

The transition from occasional to compulsive drug use and the persistent vulnerability to relapse are due to neuroadaptations in brain circuits implicated in reward, memory, drive, and control



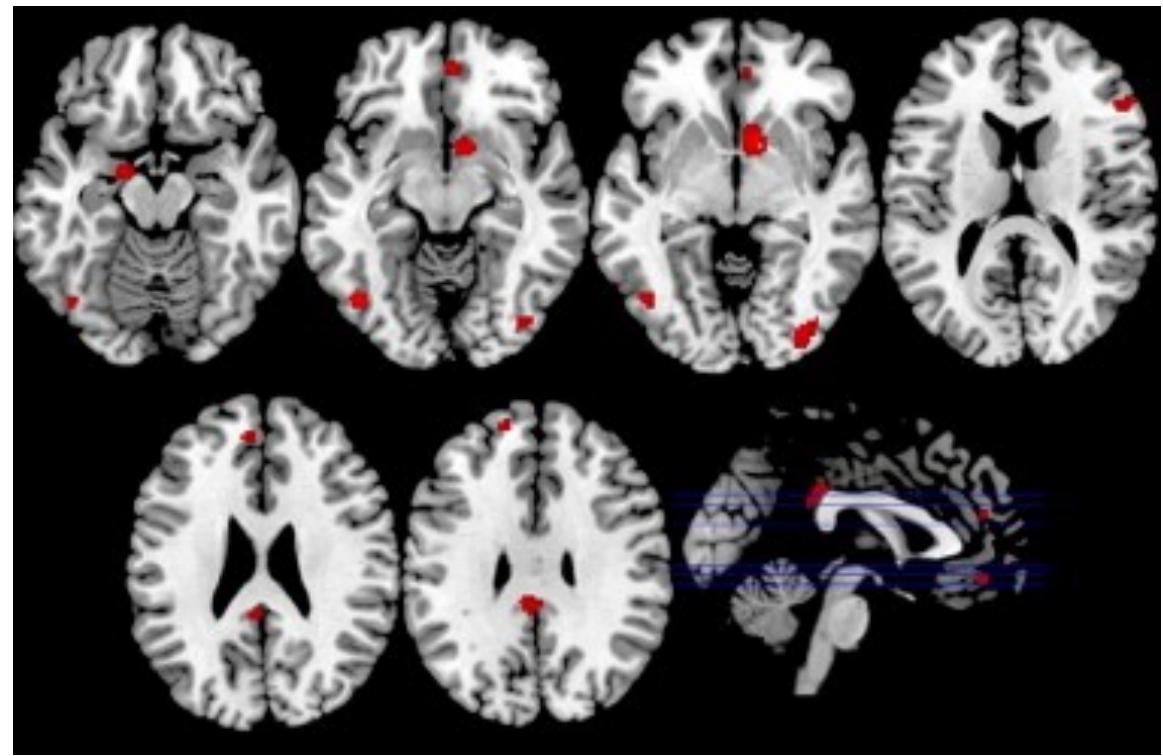
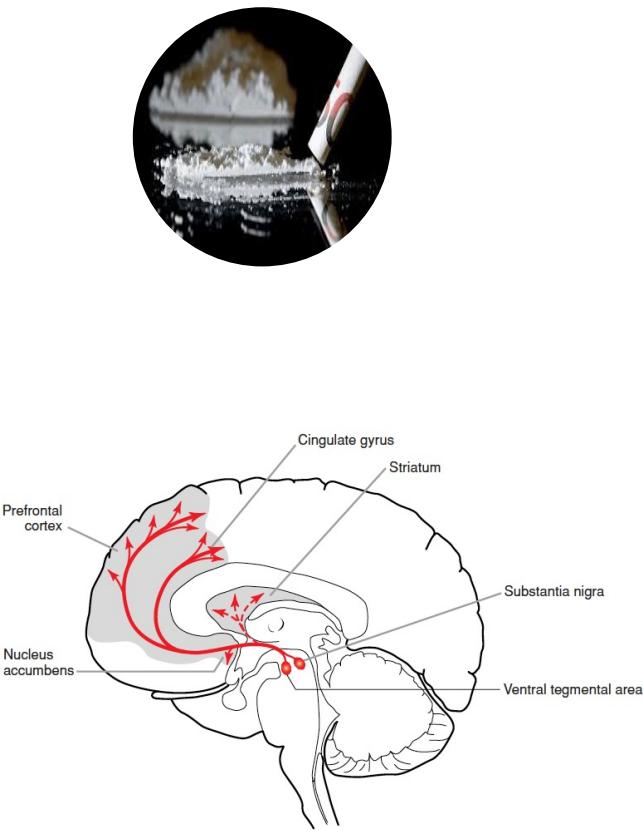
From Heinz et al., 2017

Reduced sensitivity to social rewards in cocaine users



Preller et al., PNAS, 2014

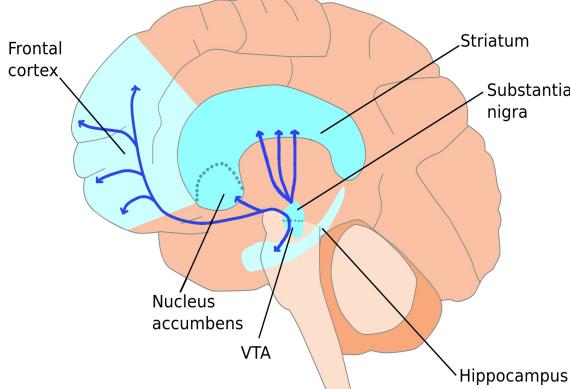
Enhanced drug-cue induced BOLD activity in individuals with SUD



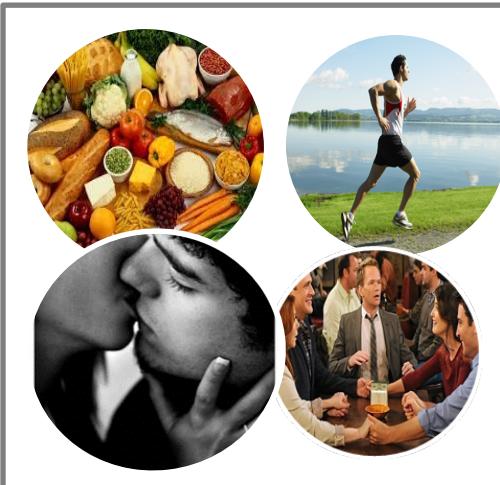
Chase, 2011

Changes within reward circuitry in addictive disorders

Brain reward (dopamine) pathways



Devaluation of non-drug related reinforcers



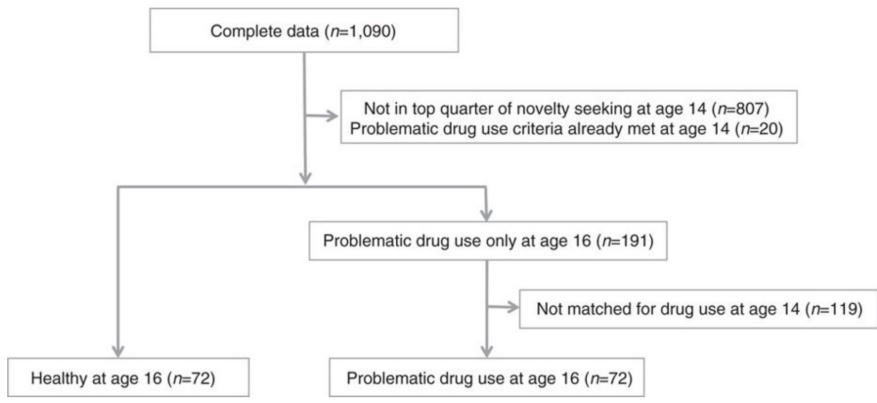
Enhanced sensitivity to drug related cues



ICD/DSM:

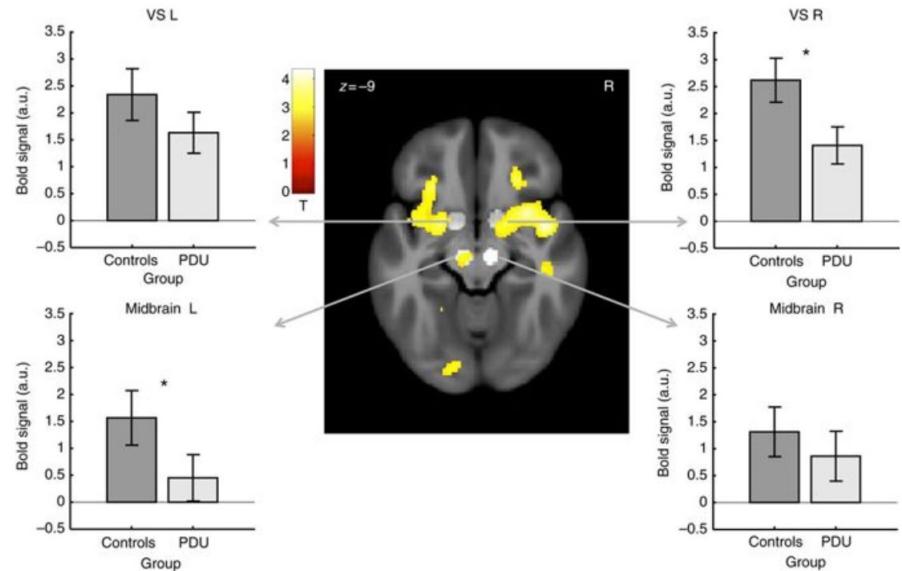
- Craving
- important alternative pleasures or interests being given up

Blunted ventral striatal responses to anticipated rewards foreshadow problematic drug use in novelty-seeking adolescents



Out of 1090 subjects with full datasets, the top quarter of novelty seekers who had not already met criteria for problematic drug use at age 14 were selected. Those who showed problematic drug use at age 16 were matched with those who did not with respect to drug use at age 14 ($n=72$ per group, 144 total).

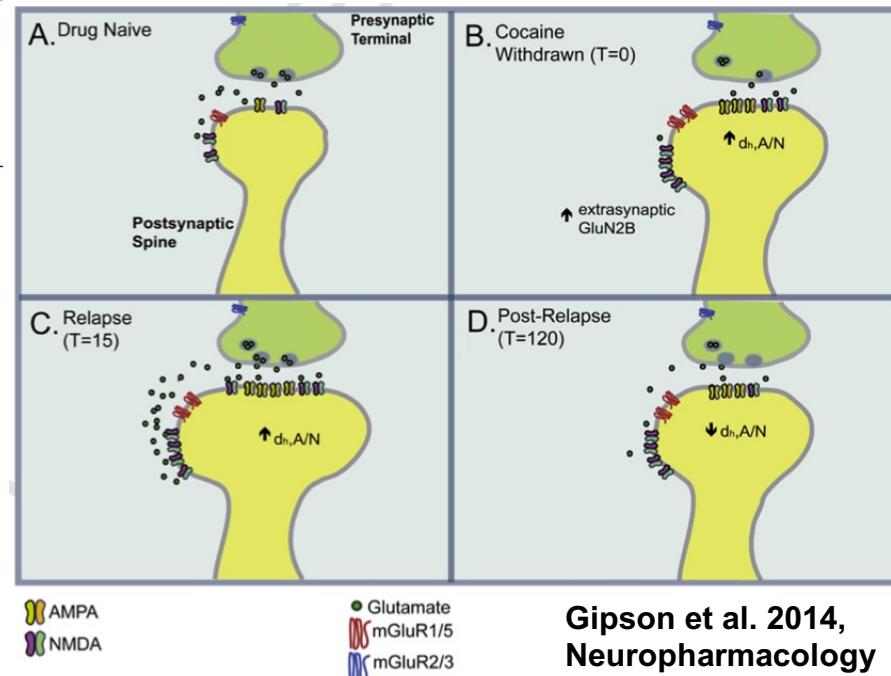
Figure 2: Subcortical brain activity in anticipation of large versus small gains for control subjects ($n=72$) versus problematic drug users ($n=72$).



The glutamate homeostasis hypothesis of addiction

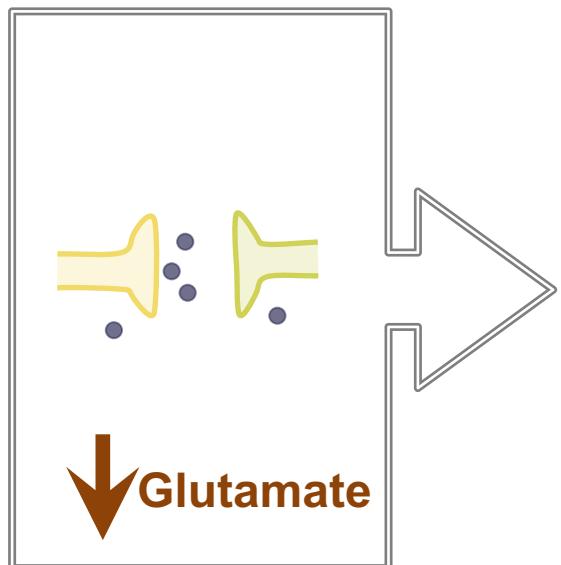
Peter W. Kalivas

Abstract | Addiction is associated with neuroplasticity in the corticostriatal brain circuitry that is important for guiding adaptive behaviour. The hierarchy of corticostriatal information processing that normally permits the prefrontal cortex to regulate reinforcement-seeking behaviours is impaired by chronic drug use. A failure of the prefrontal cortex to control drug-seeking behaviours can be linked to an enduring imbalance between synaptic and non-synaptic glutamate, termed glutamate homeostasis. The imbalance in glutamate homeostasis engenders changes in neuroplasticity that impair communication between the prefrontal cortex and the nucleus accumbens. Some of these pathological changes are amenable to new glutamate- and neuroplasticity-based pharmacotherapies for treating addiction.

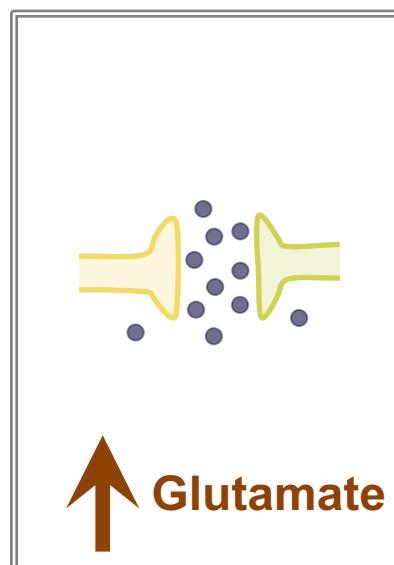


Gipson et al. 2014,
Neuropharmacology

Withdrawn



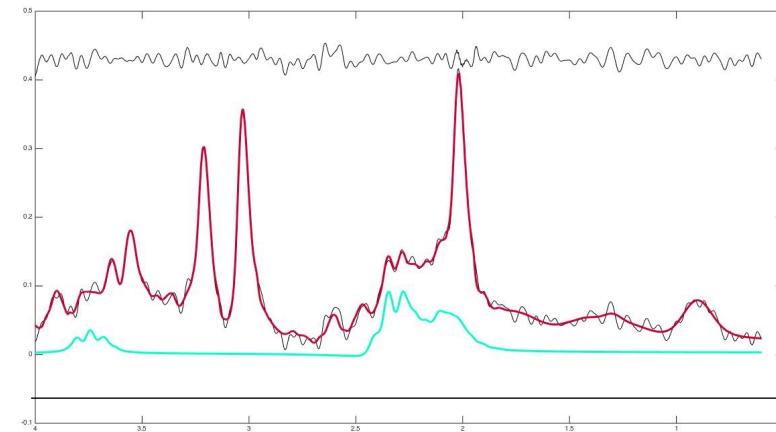
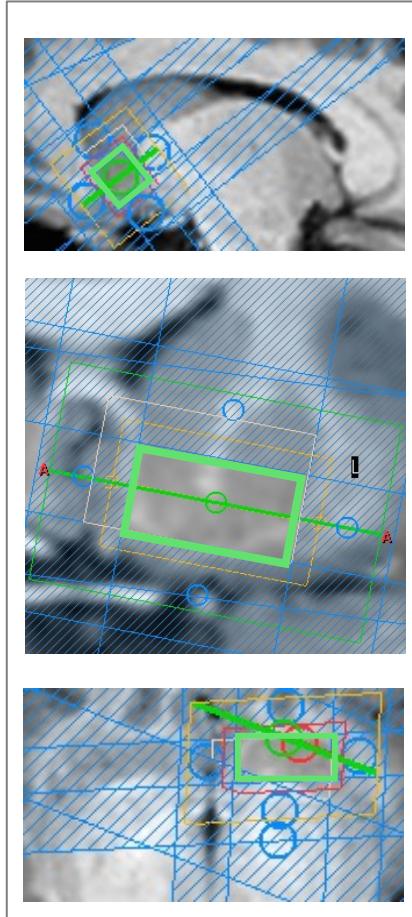
Craving/Relapse state



Glutamate levels in the Nucleus accumbens (in rodents)

Adapted from Kalivas, NRN, 2009

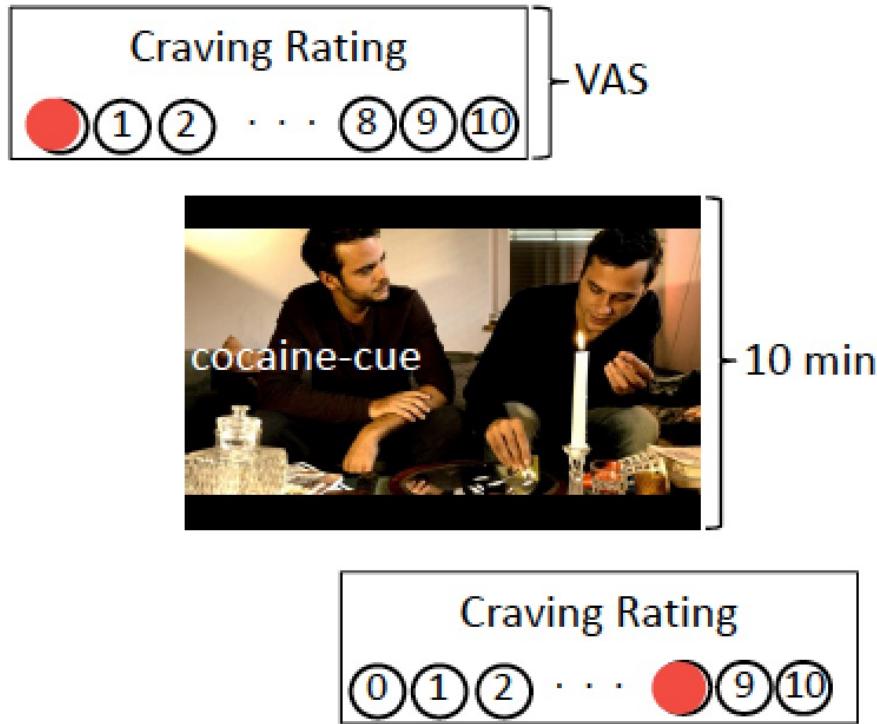
Improved MRS enables Glu Quantification in small voxels



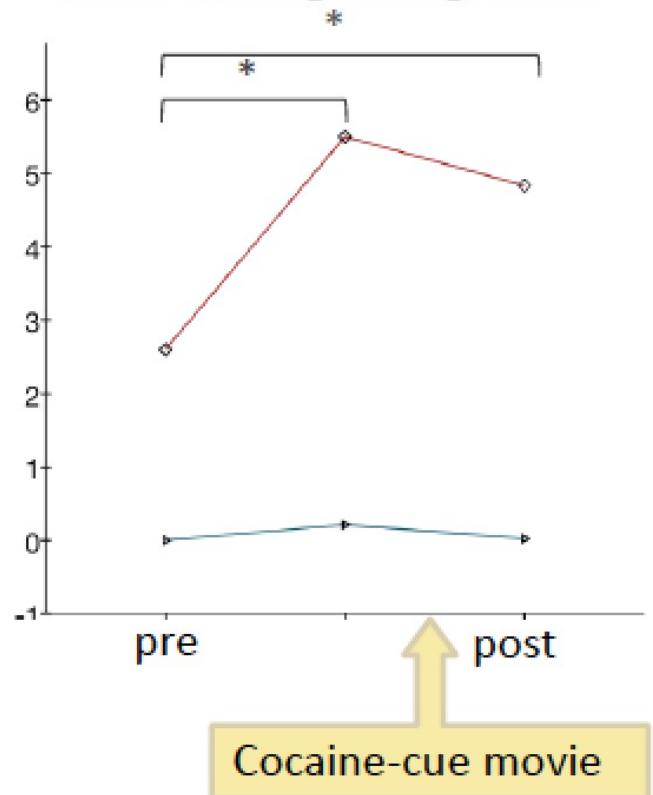
	Mean	Min.	Max.
SNR	17.09	12	22
Line width Hz	7.01	4.85	9.71
CRLB	4.91 %	4 %	7 %

Optimised MRS protocols (PRESS, non-water-suppressed, metabolite cycling, drive scale; Hock et al. 2013, 2014, 2016; Zoelch in prep.): good signal in Nucl. Accumbens ; absolute Glu quantification

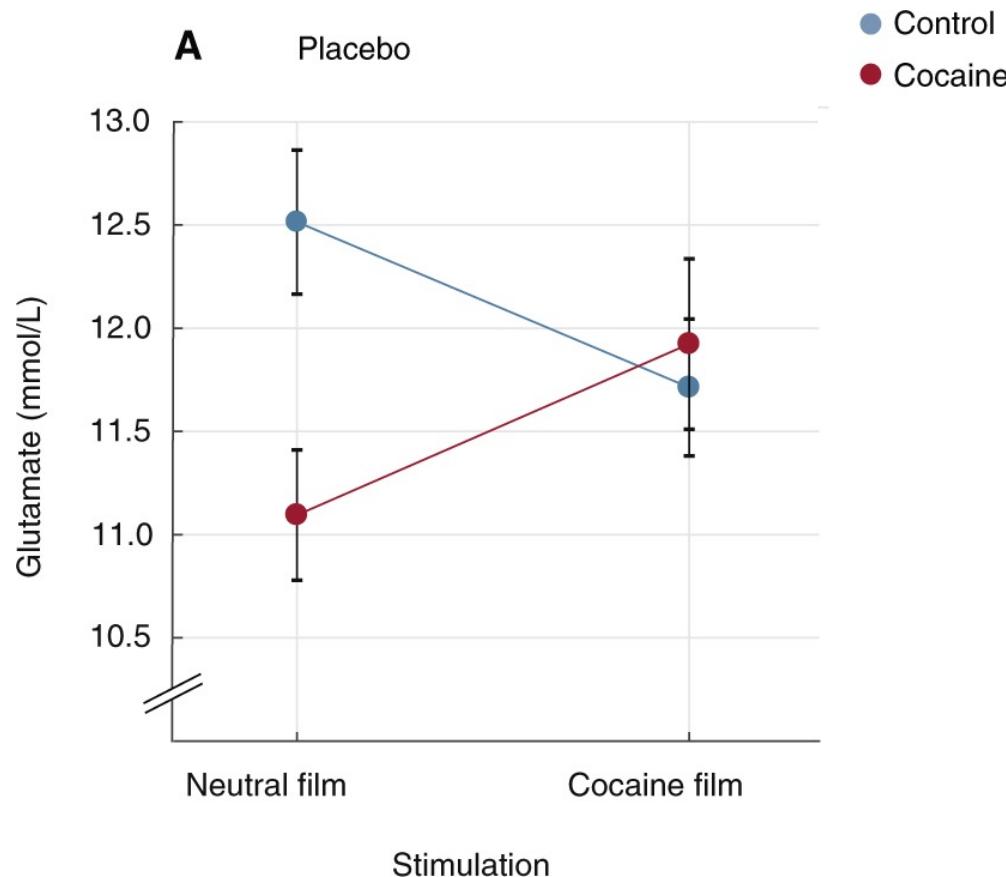
Craving Induction Paradigm



Mean Craving Ratings [VAS]

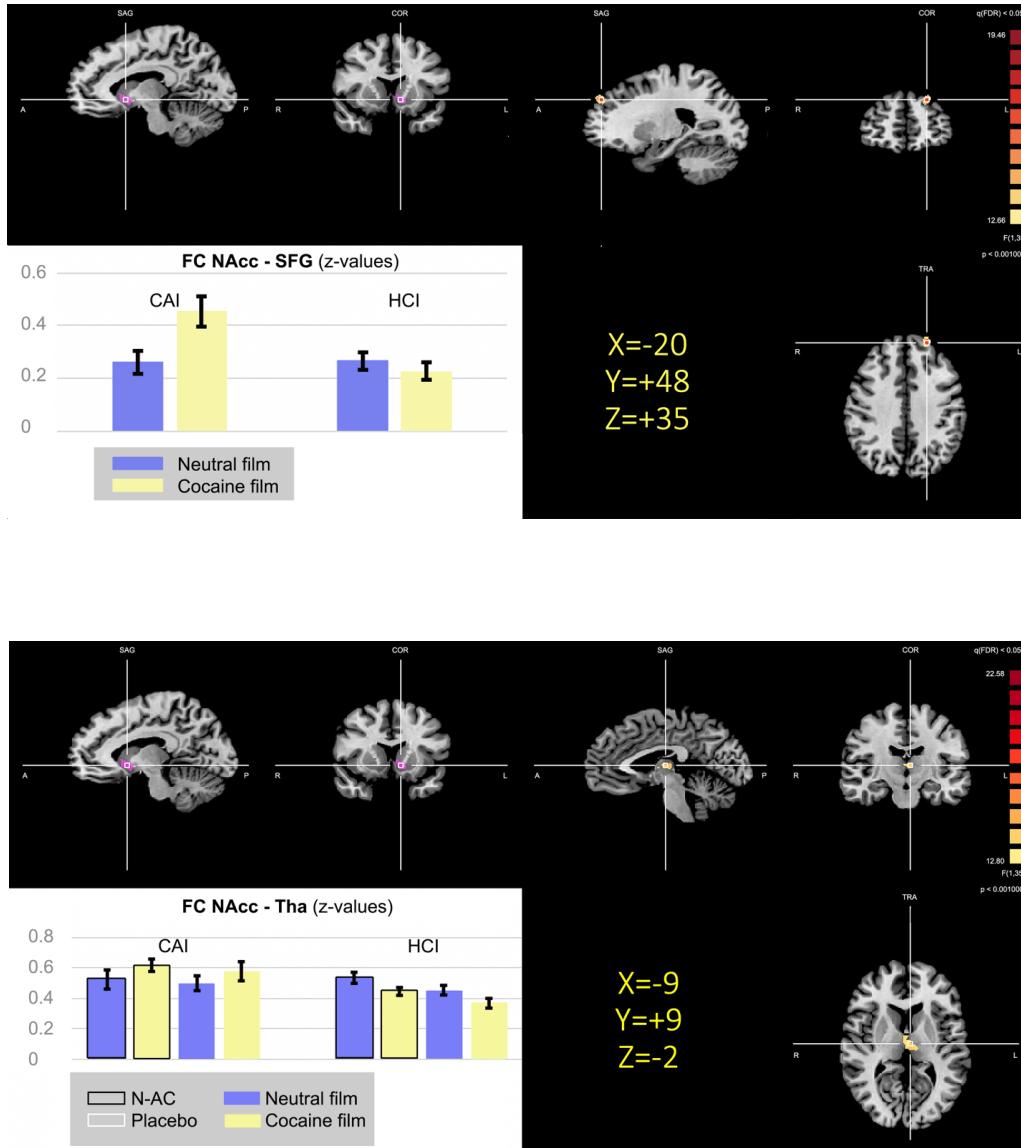


Glutamate Homeostasis in the Human Nucl. Accumbens in Cocaine Addiction



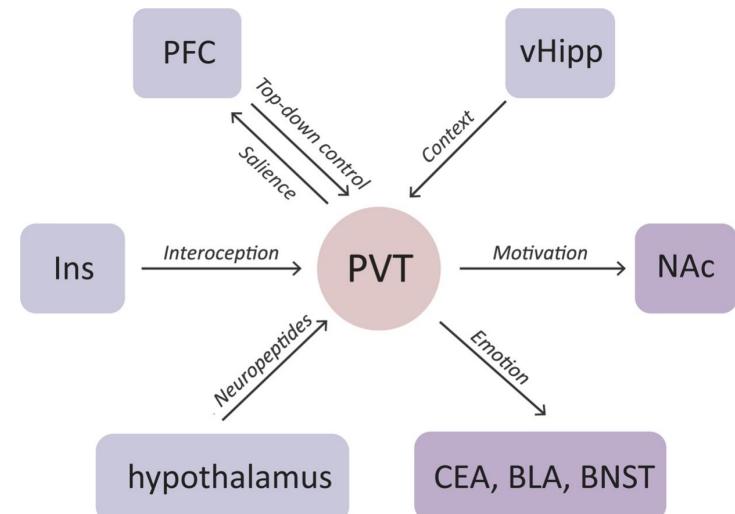
Engeli et al., Molecular Psychiatry, 2020

Craving-related changes on the network level (rsfMRI)



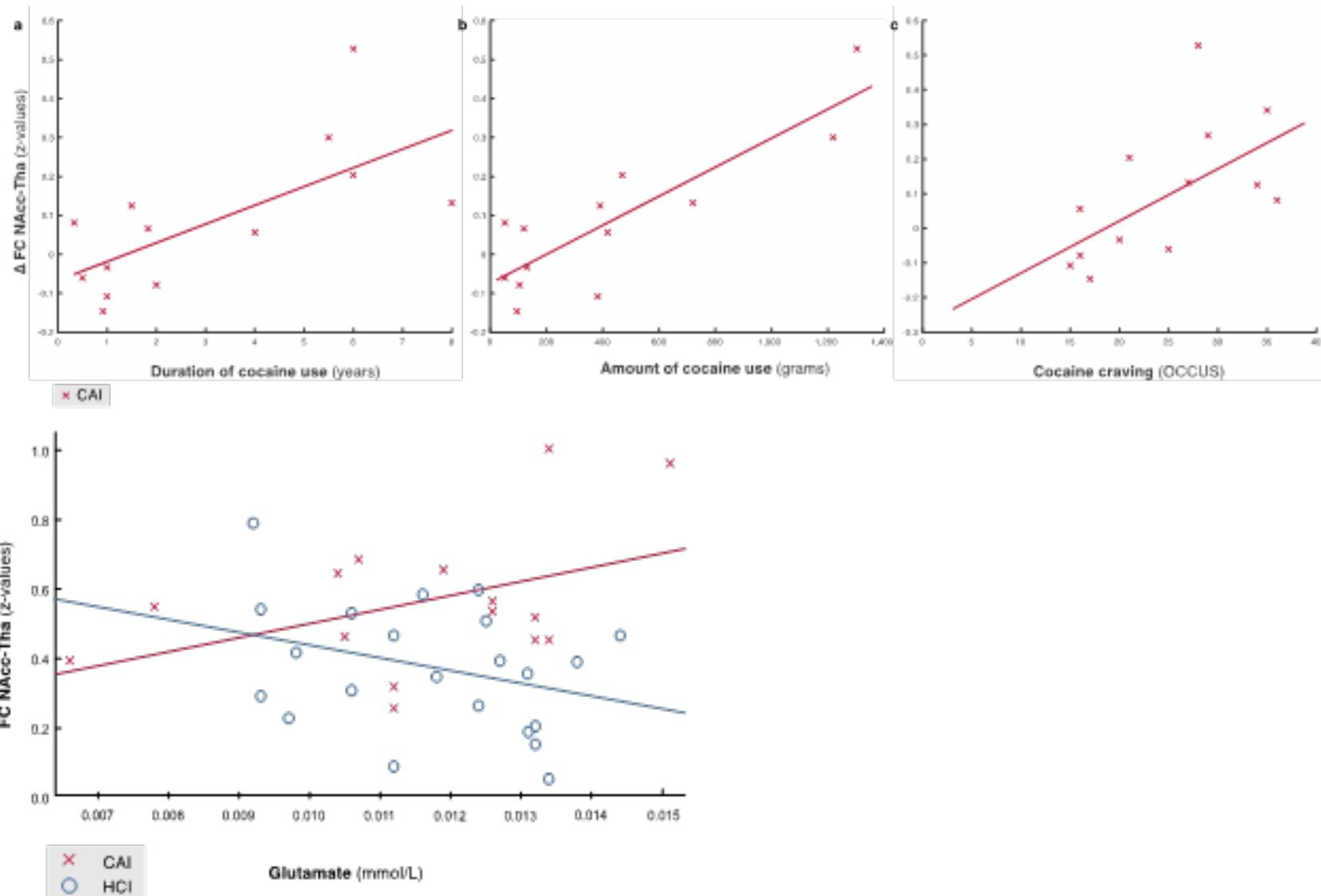
Engeli et al., submitted

The paraventricular thalamic nucleus: A key hub of neural circuits underlying drug addiction

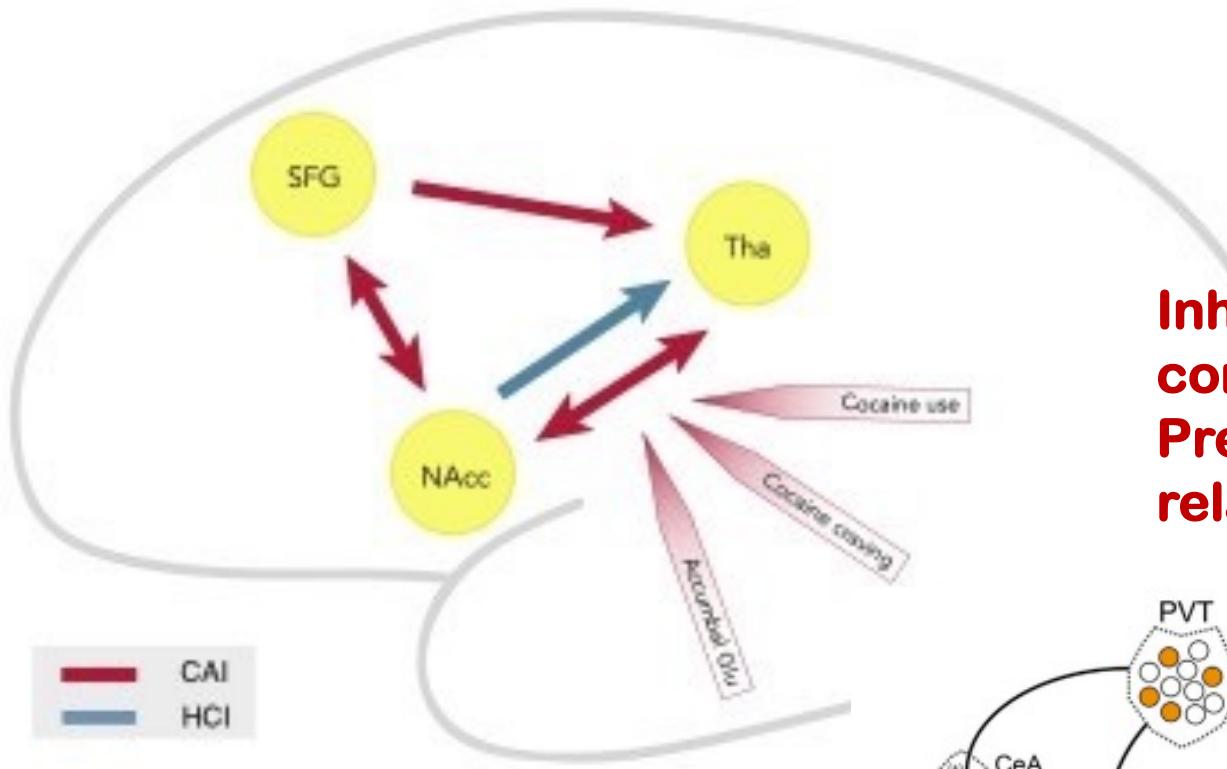


Zhou et al., 2019, Pharmacological Research

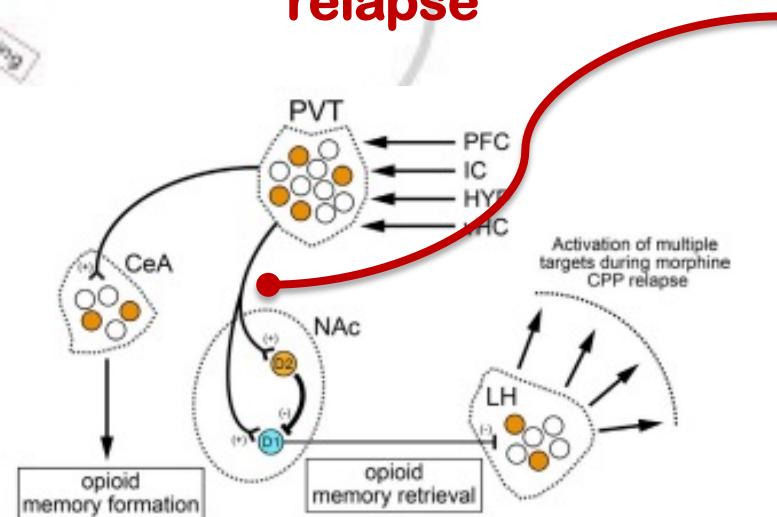
Changes in FC between Nacc and Thal correlate with disease severity and accumbal glutamate



Neurobiological correlates of craving



**Inhibition of Nacc-Thal connectivity
Prevents cue-primed relapse**

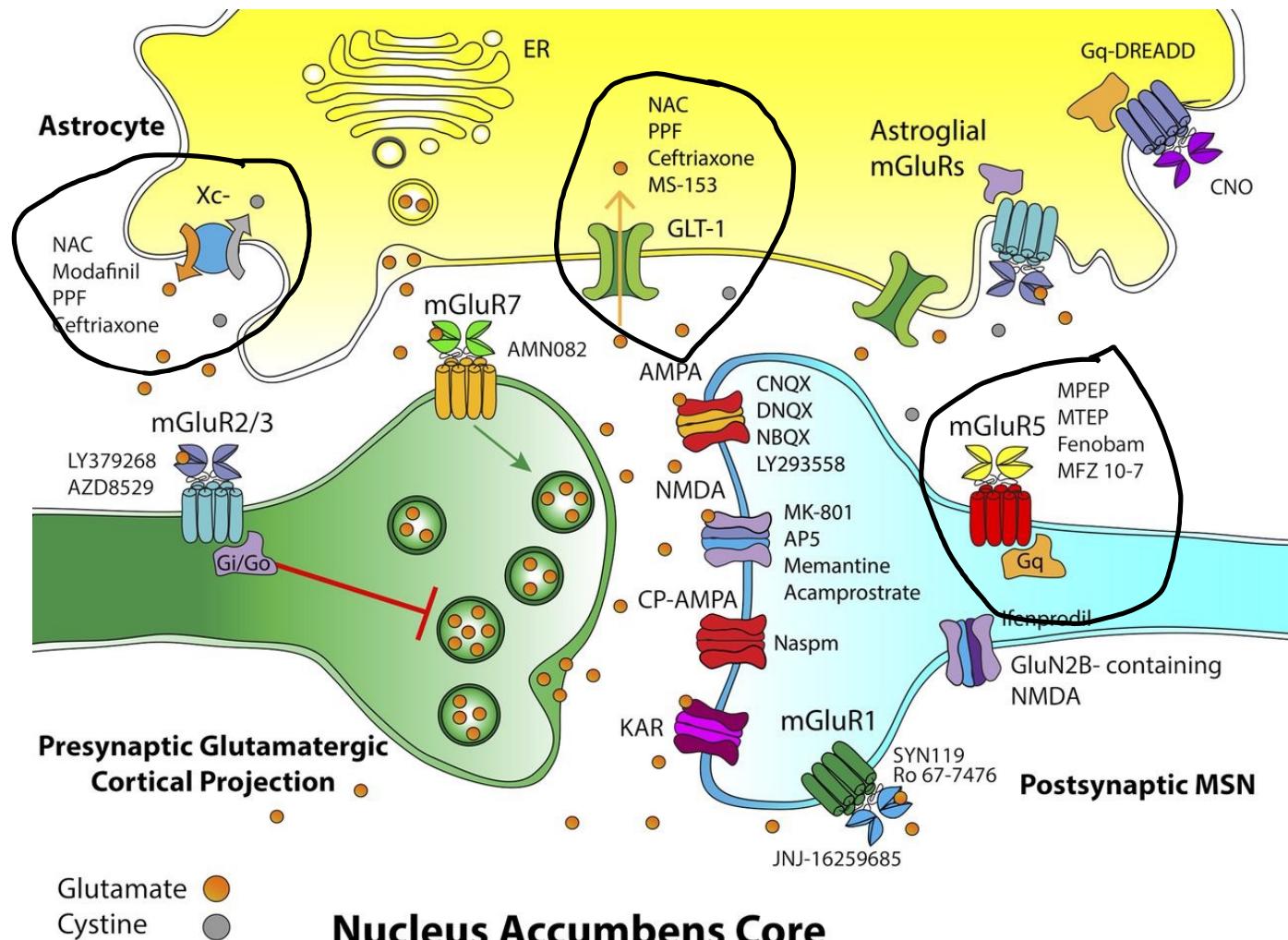


Engeli et al., submitted

Figure 1. Neural Circuit Model of PVT Control over Opioid Memory Formation and Retrieval

Keyes et al., Neuron, 2020

Pharmacological targets at the glutamatergic NAcore synapse.



M. D. Scofield et al., *Pharmacol Rev*, 2016



PHARMACOLOGICAL
REVIEWS

Summary / Questions

- *Use of psychotropic substances is common and significantly contributes to global disease burden; only a minority of users becomes addicted (multifactorial etiology)*

Who is at risk for becoming addicted? → Targeted preventive interventions

- *Current categorical classifications are well suited for identification of individuals with clinically significant dysfunction (high validity and reliability); however, binary classifications are not suited to characterise the heterogeneity of SUD well enough in order to further improve etiological understanding, therapy, and prediction of outcome;*

How can we better „describe“ affected individuals across different domains (bio-psycho-social) and across different levels within domains (molecular, circuit, behavioral)?

Can a multidimensional characterisation enable prediction of treatment response and relapse for individuals? → Targeted, stratified therapy

- *Good animal models of addiction (as compared to other psychiatric conditions)*

Can CP help to ease the transfer of knowledge from animal models to clinics?